ORIGINAL ARTICLE

Usefulness of Fatty-meal Stimulated Gallbladder Contractility by Ultrasonography in the Diagnosis of Acute Cholecystitis

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Background: Sonographic diagnosis of acute cholecystitis remains equivocal at times. The variance of gallbladder ejection fraction may be useful in diagnosis. This study evaluated the ejection fraction difference between cholecystitis patients and a control group, and also determined the diagnostic cutoff level.

Patients and Methods: Twenty patients with a diagnosis of acute cholecystitis, subsequently confirmed by pathologic findings after cholecystectomy, and 20 control patients with asymptomatic gallbladder stones were included in this study. A commercial formula, 475 Kcal with 43% lipids, was used for the test meal. All subjects received serial sonography to analyze gallbladder volume and ejection fraction before and 15, 30, 45 and 60 minutes after the test meal.

Results: Before the test meal, the mean gallbladder volume of the cholecystitis group was larger than that of the control group (54.5 mL *vs.* 20.1 mL, $p = 0.002$). The cholecystitis group had significantly lower ejection fraction than the control group at all time points after the test meal (15 minutes, –7.8% *vs.* 48.4%; 30 minutes, –0.9% *vs.* 65.8%; 45 minutes, 6.5% *vs.* 62.7%; 60 minutes, 6.6% *vs.* 71.4%; $p < 0.001$). Using 40% ejection fraction as the cutoff level, patients with cholecystitis could be differentiated entirely from the control group at 45 or 60 minutes after the test meal.

Conclusion: Patients with acute cholecystitis have bigger gallbladder volume before a meal and lower ejection fraction after a fatty meal, compared with controls. From 45 to 60 minutes after a fatty meal, 40% ejection fraction can be used as the cutoff level to differentiate patients with acute cholecystitis from those who do not.

KEY WORDS — acute cholecystitis, gallbladder ejection fraction, ultrasonography

■ *J Med Ultrasound* 2005;13(4):179–185 ■

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Introduction

Diagnosis of acute cholecystitis is usually made by clinical symptoms and ultrasound. Findings such as gallbladder wall thickening, focal pericholecystic fluid accumulation or positive sonographic Murphy's sign are considered to be signs of acute cholecystitis. However, for some patients without severe symptoms, there is no single sonographic finding that carries sufficient weight to establish or exclude the diagnosis. The rate of diagnostic accuracy depends on the operator's experience and varies widely from 48% to 91% [1–4]. At present, ultrasound is widely used by front-line physicians as the main diagnostic tool. Nevertheless, although the accurate diagnostic rate using ultrasound is more than 90% by experienced gastroenterologists, the rate is only 46% by emergency physicians due to their limited experience [2]. Moreover, cholescintigraphy can be used to confirm difficult cases of cholecystitis, with a high accuracy rate of 86–90% [4,5], but this nuclear medicine test is not available in many local hospitals or emergency rooms. Only a small fraction of equivocal cases are referred for cholescintigraphic confirmation [3,6]. The diagnosis of acute cholecystitis remains a challenge for front-line physicians.

Most acute cholecystitis is caused by stone impaction of the cystic duct, subsequently inducing gallbladder wall inflammation, edema, and thickening. Normally, stored bile in the gallbladder is ejected after a meal to aid fat digestion. The ejection fraction is usually more than 70% after a high-fat meal. However, in patients with cholecystitis, both cystic duct impaction and gallbladder inflammation may impair gallbladder ejection fraction. Since fatty-meal stimulated ultrasound is able to evaluate gallbladder ejection fraction as well as scintigraphy can, it has the potential to be a simpler tool that can improve the accuracy of cholecystitis diagnosis [7]. We conducted this study to evaluate the difference in gallbladder ejection fraction between patients with acute cholecystitis and those with asymptomatic gallbladder stones, and also aimed to determine a diagnostic cutoff level.

Patients and Methods

Inclusion and exclusion of patients

Patients with acute onset of right upper abdominal pain, tenderness and fever were scheduled for abdominal ultrasonography if acute cholecystitis was suspected. The sonographic criteria used to identify acute cholecystitis included gallbladder wall thickening, pericholecystic fluid accumulation, gallbladder stone, and sonographic Murphy's sign. By clinical symptoms and sonographic findings, an experienced gastroenterologist made the initial diagnosis of acute cholecystitis. For patients who were highly suspected of having cholecystitis, a surgeon was consulted for emergency cholecystectomy. If, because of the patient's initial poor medical condition, the surgeon did not recommend emergency operation, then the patient was scheduled for percutaneous transhepatic gallbladder drainage to relieve clinical symptoms and enrolled into this study. Following the emergency gallbladder drainage, cholecystectomy was performed within 1 week. The diagnosis of cholecystitis was further confirmed by surgical and histologic findings. The criteria for acute cholecystitis were defined as grossly congested, hemorrhagic and edematous gallbladder wall, and histologic neutrophil infiltration with hemorrhage into the mucosa. Age and gender-matched asymptomatic gallbladder stone patients were included as the control group. Their gallstones were incidentally found during routine health examinations.

Study design

Each subject was scheduled for ultrasonography to evaluate gallbladder ejection fraction. The study procedure and purpose were explained to all patients, and informed consents were obtained. A commercial high-fat formula, Nepro® (Abbott Laboratories, Chicago, IL, USA), was used as the test meal. It contains 475 Kcal in 237 mL, including 43% lipids, 14% protein, and 43% glucose. All subjects, whether in the cholecystitis or control group, drank the test meal within 3 minutes after 3–4 hours of fasting. Subjects underwent serial sonography (Nemio-20 scanner with 3.75 MHz

convex probe; Toshiba, Tokyo, Japan) to measure their gallbladder volume before the test meal and 15, 30, 45 and 60 minutes after the test meal. The series gallbladder ejection fractions after the test meal were also calculated.

During ultrasound, the greatest length (L), greatest transverse width (W), and greatest anteroposterior diameter (A) of the gallbladder were measured. The series gallbladder volumes were calculated by the following prolate ellipsoid volume formula [8]:

$$\text{Volume (V)} = 0.52 \times L \times W \times A$$

The gallbladder ejection fraction (EF) for each examination was obtained from two-volume data using the following equation [9]:

$$\text{EF (\%)} = \frac{V_0 - V_n}{V_0} \times 100\%$$

where V_0 = gallbladder volume before the test meal, V_n = series gallbladder volumes after the test meal, and n = 15, 30, 45 or 60 minutes.

Statistical analysis

Baseline demographic data between the two study groups were analyzed using Student's *t* test or Pearson's χ^2 test. Series gallbladder volumes and ejection fractions between the two study groups were analyzed using Student's *t* test. All tests of significance were two-tailed with statistical significance set at $p < 0.05$.

Results

A total of 20 patients with acute cholecystitis (7 female, 13 male) were enrolled into the cholecystitis group, and 20 asymptomatic cholelithiasis patients (8 female, 12 male) were enrolled into the control group. The mean age was 62.9 ± 20.1 years in the cholecystitis group and 58.2 ± 19.3 years in the control group (p = NS, not significant). The mean body weight and body height were also similar between the two groups (p = NS).

In the cholecystitis group, all 20 patients had gallbladder stones, 11 had gallbladder wall thickening, five had pericholecystic fluid accumulation, and 12 had sonographic Murphy's sign. The clinical symptoms and ultrasound findings of each cholecystitis patient are shown in Table 1. All diagnoses of cholecystitis were further confirmed by operative findings and histology. In contrast, while all patients in the control group had gallbladder stones, none had gallbladder wall thickening, fluid accumulation or local tenderness. After drinking the test meal, a series of ultrasound scans were performed every 15 minutes up to 1 hour. Throughout the period of examination, no patient suffered from acute abdominal pain or vomiting in either the cholecystitis or control group.

As shown in Table 2, patients in the cholecystitis group had larger gallbladder volumes than control group subjects, both before and after the test meal ($p < 0.01$). In the control group, gallbladder volume post-test meal was significantly decreased compared with the fasting volume ($p < 0.001$). In contrast, patients with acute cholecystitis demonstrated no significant change in gallbladder volume after the test meal, even up to 60 minutes (p = NS).

Gallbladder ejection fractions were significantly different between the two study groups at all time points after the test meal (Fig.). The mean ejection fraction of the control group was 48.4% at 15 minutes after the test meal, and had progressively increased to 71.4% by 60 minutes after the meal. In contrast, the mean gallbladder ejection fractions of the cholecystitis group remained less than 10% throughout, even at 60 minutes after the test meal (Table 2).

The sensitivity and specificity at different cutoff values and at different times when using gallbladder ejection fraction to recognize acute cholecystitis are listed in Table 3. Using 40% as the cutoff value at 45 minutes or 35%, 40% and 45% at 60 minutes after the meal, the sensitivity and specificity achieved were as high as 100%. On the other hand, best accuracy was achieved using 40% ejection fraction between 45 to 60 minutes after the test meal as the cutoff point.

Table 1. Clinical symptoms and ultrasound features of each patient in the cholecystitis group

Patient	Clinical symptoms		Gallbladder ultrasound findings			
	Fever	Right upper abdominal pain	Gallstone	Gallbladder wall thickening	Murphy's sign	Pericholecystic fluid accumulation
1	+		+	+	+	+
2	+	+	+		+	
3	+	+	+	+		
4	+	+	+		+	
5	+		+		+	
6	+	+	+	+	+	
7	+	+	+		+	
8	+	+	+	+	+	+
9	+	+	+	+		
10	+	+	+		+	
11	+	+	+			+
12	+	+	+		+	
13	+		+		+	
14	+	+	+	+		
15	+	+	+			
16	+		+	+		+
17		+	+	+	+	
18	+	+	+	+		
19	+	+	+	+	+	+
20	+	+	+	+		

Table 2. Series gallbladder volumes and ejection fractions before and after fatty meals

	Volume (mL)			Ejection fraction (%)		
	Cholecystitis	Control	*p**	Cholecystitis	Control	*p**
Time after fatty meal (min)						
0	54.5 ± 30.4	20.1 ± 8.3	0.002	–	–	–
15	57.4 ± 31.9	9.2 ± 4.3†	< 0.001	–7.8 ± 26.4	48.4 ± 25.6	< 0.001
30	52.4 ± 25.7	6.4 ± 3.5†	< 0.001	–0.9 ± 22.8	65.8 ± 19.3	< 0.001
45	47.3 ± 19.6	7.2 ± 4.5†	< 0.001	6.5 ± 21.8	62.7 ± 16.7	< 0.001
60	48.3 ± 24.0	5.9 ± 4.7†	< 0.001	6.6 ± 21.9	71.4 ± 13.3	< 0.001

**Comparison of gallbladder volume and ejection fraction between the two study groups either before or 15–60 minutes after test meal (Student's t test); †p < 0.001 (Student's t test) when comparing gallbladder volume between the two study groups before test meal.*

Discussion

Several published studies demonstrate that gallbladder volume and ejection fraction are different between cholecystitis patients and healthy subjects [10–12]. Fatty-meal stimulated cholescintigraphy, instead of cholecystokinin-stimulated, has been studied to evaluate gallbladder motility and select gallbladder dysfunction patients for cholecystectomy [13–15]. Furthermore, fatty-meal stimulated

sonography can also be used in the diagnosis of chronic acalculous cholecystitis in children. A study concluded that gallbladder ejection fraction less than 35% at 30 minutes after meal challenge may be useful in the diagnosis of acalculous cholecystitis, benefiting children with the use of cholecystectomy [16]. These studies indicate that fatty-meal stimulated ultrasonography is useful for evaluating gallbladder dysfunction and selecting acalculous cholecystitis patients for operation.

In this study, series gallbladder volumes were analyzed after fatty-meal stimulation to evaluate its role in the diagnosis of acute stone-related cholecystitis. Gallbladder emptying function was significantly different after a test meal between cholecystitis patients and controls. Using 40% as the cutoff level for 45-minute ejection fraction, patients with acute cholecystitis were well differentiated from patients without. At 60 minutes after a test meal, a 35–45% cutoff level is useful for distinction. Using a 40% ejection fraction as the cutoff level, cholecystitis patients were well-differentiated from the control group at 45–60 minutes after the test meal, indicating that, in clinical practice, a second-look sonography could be performed within a 15-minute window without a decrease in diagnostic efficacy. Accordingly, if the diagnosis of acute cholecystitis cannot be confirmed by ordinary ultrasound, then fatty-meal stimulated ultrasonography would be a useful tool for front-line physicians.

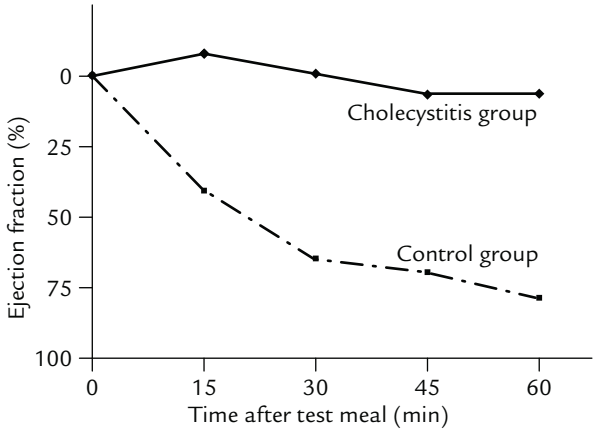

Fig. *Post-fatty meal gallbladder ejection fractions in the two study groups. The control group has significantly higher mean ejection fraction than the cholecystitis group, from 15 to 60 minutes after the test meal.*

However, this study had some limitations. It only included 20 cholecystitis patients and 20 control patients: the case number was limited. Moreover, the acute-stressed hospitalized patients may have poorer gallbladder ejection fraction than normal subjects, possibly influencing the diagnostic accuracy of fatty-meal ultrasound. In this study, only asymptomatic outpatients were included in the control group. Due to these limitations, further prospective and large-scale studies should be conducted to

Table 3. Sensitivity and specificity in recognizing acute cholecystitis by gallbladder ejection fraction at different cutoff values

	Values of gallbladder ejection fraction to define acute cholecystitis					
	<25%	<30%	<35%	<40%	<45%	<50%
Time after fatty meal						
15-min sensitivity (%)	85	90	100	100	100	100
15-min specificity (%)	90	90	85	75	60	55
30-min sensitivity (%)	85	85	90	90	100	100
30-min specificity (%)	100	100	90	80	80	75
45-min sensitivity (%)	75	75	75	100	100	100
45-min specificity (%)	100	100	100	100	90	65
60-min sensitivity (%)	60	65	100	100	100	100
60-min specificity (%)	100	100	100	100	100	90

confirm these results. However, these preliminary data do indicate a cutoff level and time frame for performing second-look sonography, which is a useful starting point to support further clinical study.

In daily clinical practice, abdominal ultrasonography is usually performed after 8 hours fasting. However, a 3–4 hour fast may be enough to analyze gallbladder ejection fraction because the gallbladder refills after a 2–3 hour fast [17]. Therefore, in this study, ultrasonography was performed 3–4 hours after the test meal to enable an earlier diagnosis. Moreover, patients are usually kept fasting if acute cholecystitis is suspected because meal intake may induce gallbladder contraction and exacerbate the pain. However, in this study, no patient in the cholecystitis group experienced pain after drinking the test meal. This result implies that the fatty meal did not induce gallbladder contraction in the cholecystitis patients. The reasonable explanation for this is that acute cholecystitis may impair contractility function, and the gallbladder did not contract in these patients after the test meal [12].

As cholescintigraphy is usually time-consuming, cholecystokinin infusion or morphine augmented scintigraphy have been administered in the recent past to overcome this shortcoming and improve diagnostic accuracy [18,19]. Since morphine can promote gallbladder contraction, further study should focus on the use of morphine, rather than fatty test meals, in the evaluation of gallbladder ejection fraction and the diagnosis of cholecystitis.

It may be supposed that only gallbladder volume needs to be evaluated for accurate diagnosis because gallbladder volumes were shown to be significantly different between the two study groups. However, gallbladder size is positively correlated with age, height, body weight, and body surface area [8]; these individual variations will influence diagnostic accuracy. Thus, using ejection fraction to compare the gallbladder volume change of each patient can reduce the interfering influence of such variations.

In conclusion, patients with acute cholecystitis have greater gallbladder volumes when fasting and lower ejection fractions after fatty meals, compared with control subjects who do not have acute cholecystitis. At 45–60 minutes after a fatty meal, a 40% ejection fraction can be used as a cutoff level to differentiate between these two groups. These data can help front-line physicians diagnose acute cholecystitis and form a basis for future study.

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